

WHAT IS CLAIMED IS:

1. A process for the production of a peptide having the structure

5 X-AA₁-AA₂.....AA_n-Y

wherein AA is an L- or D-amino acid residue,

X is hydrogen or an amino protective group

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Y is OH, NH₂ or an amino acid sequence comprising from 3 to 9 amino acid residues and n is an integer greater than 2 by solid phase synthesis comprising

(a) coupling the C-terminal amino acid in the form of an N-alpha-protected reactive derivative to the support optionally by means of a linker, wherein said C-terminal amino acid comprises a presequence comprising from 3 to 9 amino acids

independently selected from native L-amino acids having a side chain functionality which is protected during the coupling steps and having a propensity factor P_α > 0.57 and a propensity factor P_β ≤ 1.10 or the corresponding D-amino acids;

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20 (b) adding subsequent amino acids forming the peptide sequence by stepwise coupling or coupling as a peptide fragment in the form of protected fragments;

(c) removing the protecting groups from the peptide sequence of (b) and

25 (d) optionally cleaving the presequence from the formed peptide.

2. The process according to claim 1, wherein the presequences have from 5 to 7 amino acid residues.

3. The process according to claim 1, wherein the C-terminal amino acid is side-chain protected.

5 4. The process according to claim 1, wherein the amino acids forming part of the presequence are independently selected from the group consisting of Lys, Glu, Asp, Ser, His, Asn, Arg, Met and Gln.

10 5. The process according to claim 1, wherein the amino acids in the presequence are either exclusively Lys or Glu or a sequence (Glu)_q(Lys)_p, where $p + q$ is 3 to 9, and the order of Lys and Glu is arbitrarily chosen.

15 6. The process according to claim 1, wherein the amino acids in the presequence are a sequence (Glu)_q(Lys)_p, where $p + q$ is 6 to 9, and the order of Lys and Glu is arbitrarily chosen.

7. The process according to claim 1, wherein the N- α amino protective group is Fmoc or Boc.

20 8. The process according to claim 1, wherein the amino acids in the presequence are chosen from amino acids having a side chain functionality selected from the group consisting of a carboxy, carboxamido, amino, hydroxy, guanidino, sulphide and imidazole moiety.

25 9. The process according to claim 1, wherein the solid support is a functionalized resin selected from the group consisting of polystyrene, polyacrylamide, polyethyleneglycol, cellulose, polyethylene, latex and dynabeads.

10. The process according to claim 1, wherein the C-terminal amino acid is attached to the solid support by means of a common linker selected from the group consisting of 2,4-dimethoxy-4-hydroxy-benzophenone, 4-(4-hydroxymethyl-3-methoxyphenoxy)-butyric acid (HMPB), 4-hydroxymethylbenzoic acid, 5 4-hydroxymethyl-3-phenoxyacetic acid (HMPA), 3-(4-hydroxymethylphenoxy)propionic acid and p-[(R,S)- α (l-(9H-fluoren-9-yl)-methoxyformamido]-2,4-dimethoxybenzyl)-phenoxyacetic acid.

10 11. The process according to claim 1, wherein the peptide is cleaved from the support by means of an acid, a base or by means of photolysis.

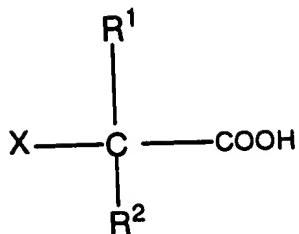
12. The process according to claim 1, wherein the peptide is cleaved from the support by means of an acid selected from the group consisting of trifluoroacetic acid (TFA), 15 trifluoromethanesulfonic acid (TFMSA), hydrogen bromide (HBr), hydrogen chloride (HCl) and hydrogen fluoride (HF).

13. The process according to claim 1, wherein the peptide is cleaved from the support by means of a base selected from the group consisting of ammonia, hydrazine, an alkoxide 20 and hydroxide.

14. The process according to claim 1, in which a linker is inserted between the presequence attached to a support and the AA₁-AA_n sequence.

25 15. The process according to claim 14, wherein the linker is optically active.

16. The process according to claim 14, wherein the linker is an α -hydroxy or α -amino acid of the general formula



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wherein X is OH or NH₂, and R¹ and R² are independently selected from H, C₁₋₃ alkyl, phenyl and substituted phenyl, where the substituents are one or more electron donating substituents chosen among C₁₋₃ alkoxy, C₁₋₃ alkyl, or two vicinal substituent groups are joined to form a 5 or 6 membered carbon ring together with the carbon atoms to which they are attached.

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17. The process according to claim 14, wherein the linker is (+)-4-methoxymandelic acid, diphenylglycine or glycolic acid.

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18. The process according to claim 1, wherein the presequence is enzymatically cleaved from the formed peptide.

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19. The process according to claim 18, wherein the enzyme is selected from the group consisting of suitable carboxy- and endopeptidases.

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20. The process according to claim 1, further comprising inserting a first linker between the presequence attached to a support and the AA₁-AA_n sequence and a second linker between the presequence and the solid support with orthogonal cleavage conditions to the first linker so the second linker is selectively cleaved by means of an acid or base to give a peptide AA₁-AA_n linked to the presequence by means of said first linker.

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21. An agent for use in solid phase peptide synthesis having the general formula X-AA'₁-...-AA'_m-Y₁-R, wherein R is a solid support applicable in solid phase peptide

synthesis, Y_1 is an amino acid sequence comprising from 3 to 9, independently selected from L-amino acids having a side chain functionality which is protected during the coupling steps and having a propensity factor $P\alpha > 0.57$ and a propensity factor $P\beta \leq 1.10$, or the corresponding D-amino acid, AA' is an L or D-amino acid residue, m is zero or an integer from 1 to 40 and X is hydrogen or an amino protective group.

22. An agent for use in solid phase peptide synthesis having the general formula $X-AA'_1-\dots-AA'_{m-1}-L_1-Y_1-R$

10 wherein R is a solid support applicable in solid phase peptide synthesis, Y_1 is an amino acid sequence comprising from 3 to 9, independently selected from L-amino acids having a side chain functionality which is protected during the coupling steps and having a propensity factor $P\alpha > 0.57$ and a propensity factor $P\beta \leq 1.10$, or the corresponding D-amino acid, AA' is an L or D-amino acid residue, m is zero or an integer from 1 to 40 and X is hydrogen or an amino protective group and L_1 is a linker which enables a selective cleavage of the bond to AA'_{m-1} .

23. An agent for use in solid phase peptide synthesis having the general formula

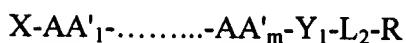
20 $X-AA'_1-----AA'_{m-1}-L_1-Y_1-L_2-R$

wherein R is a solid support applicable in solid phase peptide synthesis, Y_1 is an amino acid sequence comprising from 3 to 9 amino acid residues independently selected from L-amino acids having a side chain functionality which is protected during the coupling steps and having a propensity factor $P\alpha > 0.57$ and a propensity factor $P\beta \leq 1.10$, or the corresponding D-amino acid, AA' is an L or D-amino acid residue, m is zero or an integer from 1 to 40 and X is hydrogen or an amino protective group, L_1 is a linker which enables a selective cleavage of the bond to AA'_{m-1} and L_2 is a linker with orthogonal cleavage

conditions relative to the first linker so that it is selectively cleaved from the solid support.

24. An agent for use in solid phase peptide synthesis having the general formula

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wherein R is a solid support applicable in solid phase peptide synthesis, Y₁ is an amino acid sequence comprising from 3 to 9 amino acid residues independently selected from

10 L-amino acids having a side chain functionality which is protected during the coupling steps and having a propensity factor $P\alpha > 0.57$ and a propensity factor $P\beta \leq 1.10$, or the corresponding D-amino acid, AA' is an L or D-amino acid residue, m is zero or an integer from 1 to 40 and X is hydrogen or an amino protective group, L₂ is a linker with orthogonal cleavage conditions relative to the first linker and enabling a selective cleavage from the solid support.

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25. An agent for use in solid phase peptide synthesis having the formula



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Wherein R is a solid support applicable in solid phase peptide synthesis, Y₁ is an amino acid sequence comprising from 3 to 9 amino acids independently selected from L-amino acids having a side chain functionality which is protected during the coupling steps and having a propensity factor $P\alpha > 0.57$ and a propensity factor $P\beta \leq 1.10$, or the corresponding D-amino acid, L₁ is a linker which enables a selective cleavage of the bond to a peptide sequence and L₂ is a linker with orthogonal cleavage conditions relative to the first linker and enabling a selective cleavage from the solid support.